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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,683	06/24/1999	GREGOR CEVC	35946-701.831	2670

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
11/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/284,683	CEVC, GREGOR	
	Examiner	Art Unit	
	GOLLAMUDI S. KISHORE	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106,112-115,118,120,121,123,124,129-136 and 138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106,112-115,118,120,121,123,124,129-136 and 138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-4-09; 7-21-09, 10-22-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 10-22-09 is acknowledged.

Claims included in the prosecution are 106, 112-115, 118 and 120-121, 123-124, 129-136 and 138.

Upon consideration, the 112 rejection is withdrawn.

Claim Rejections - 35 U.S.C. § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 106, 112-115, 118 and 120-124 and 129-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheffield (4,937,254) in combination with

Radhakrishnan (5,043,165), Edger (5,498,420) by themselves or together in further combination with Mezei (4,897,269).

What is lacking in Hayward is the use of claimed antioxidants and Stabilizers.

Sheffield teaches a method of topical administration of liposomal formulations containing phosphatidylcholine and NSAID. The method of administration is topically and either internally or externally which implies skin. The composition further contains PBS and hydrocolloids (col. 3, lines 7-56; col. 6, line 15 through col. 7, line 12, Examples 13-15).

What is lacking in Sheffield is the inclusion of benzyl alcohol, stabilizers, antioxidants and the use of unilamellar vesicles of instant sizes.

Radhakrishnan while disclosing liposomal formulations teaches that multilamellar preparations can be treated to produce small unilamellar vesicles, large unilamellar vesicles or oligolamellar vesicles which are characterized by sizes in the 0.04-0.08 microns, 0.1 to 0.5 microns and mixed micron range. Radhakrishnan further teaches that the advantage of the suvs is the greater packing density of the liposomes at a mucosal surface and suvs are preferred for topical or nasal use (col. 7, line 45 through col. 8, line 14).

Edger while disclosing liposomal formulations for topical use teaches that from statistical point of view the interaction of small unilamellar vesicles with other cells is likely to be greater than that of multilamellar vesicles which facilitates the transfer of membrane constituents (col. 1, line 48 through col. 2, line 10).

Mezei while disclosing liposomal compositions teaches the addition of preservatives and antioxidants such as benzyl alcohol and tocopherol (abstract, Example 4 and col. 14, lines 42-63).

The use of small unilamellar vesicles of claimed sizes would have been obvious to one of ordinary skill in the art because of the advantages taught by Radhakrishnan and Edger. The addition of antioxidants and stabilizers in the compositions of Sheffield would have been obvious to one of ordinary skill in the art since such an addition would prevent oxidation of lipids and degradation by bacteria respectively as taught by Mezei. Sheffield also lacks the teaching of the application of the claimed amount of the liposomes on the skin surface. However, since the amount applied depends upon the condition to be treated and the severity of the condition, it is deemed obvious to one of ordinary skill in the art to manipulate this parameter to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Sheffield stresses the importance of using vesicles of 'comparatively large size' in order to aid in treatment of a patient and thus teaches away. This argument is not persuasive. As noted by applicant himself, Sheffield teaches that larger sizes are preferable in order to increase the dwell time of the vesicles containing the NSAID ***in the peritoneal cavity***. However, in view of the Sheffield's teachings of topical application which includes skin (as discussed in the previous action) one of ordinary skill in the art would be motivated to use smaller liposomes for the advantages taught by Radhakrishnan and Edger. These advantages are for topical mode as taught by these references. Applicant's arguments that Sheffield does not

teach salt of NSAID are not persuasive since as pointed out above, Example 13 of Sheffield teaches sodium salt of ibuprofen.

Applicant's arguments that Edger teaches away from the use of the 75 nm to 400 nm vesicles recited in the claims by cautioning that contrary to liposomes that are smaller than 30 nm, "large liposomes having a size of over 60 nm get caught in the upper skin layers where they release the active substance are not persuasive since instant claims do not recite the requirement that the liposomes have to enter systemically. In fact, on page 10 of specification (lines 1-3) applicant state ***that this size range is for dermatological applications***.

Applicant's arguments that Radhakrishnan and Mezei are further distinguishable from the present claims in that they each emphasize the importance of including cholesterol in the vesicles. This argument is not persuasive. First of all on page 15 of the specification (third paragraph), applicant himself indicates that cholesterol can be included. Secondly, these references have been combined for the teachings of the advantages of smaller sizes. The motivation to combine need not be the same as applicant's.

3. Claims 106, 112-115, 118 and 120-121, 123-124, 129-136 and 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelemen (5,716,526), Tremblay (5,783,210) individually or in combination, optionally in further with Sheffield (4,937,254), in further combination with Mezei (4,897,269)..

Kelemen teaches that liposomes can be made with phospholipids such as phosphatidylcholines and hydrophilic compounds can be encapsulated within the

aqueous interior and hydrophobic compounds in the lipid bilayer. Kelemen also teaches that unilamellar vesicles can be prepared by extrusion of multilamellar vesicles. The drugs which can be used include salicylic acid acetate (salt). Kelemen further teaches the use of the liposomes for ibuprofen, sulindac, piroxicam and naproxen (col. 12, line 11 through col. 13, line 42; col. 14, lines 34-59).

Tremblay similarly teaches large unilamellar liposomes containing salicylic acid acetate, ibuprofen, sulindac, piroxicam and naproxen and indomethacin. The liposomes are made with greater than 97 percent by weight of phosphatidylcholine. The method of administration includes topical mode (abstract, col. 1, lines 26-47; col. 5, line 29 through col. 7, line 8; col. 7, lines 55-68).

Sheffield teaches a method of topical administration of liposomal formulations containing phosphatidylcholine and NSAID. The method of administration is topically and either internally or externally which implies skin. The composition further contains PBS and hydrocolloids (col. 3, lines 7-56; col. 6, line 15 through col. 7, line 12, Examples 13-15).

Mezei while disclosing liposomal compositions teaches the addition of preservatives and antioxidants such as benzyl alcohol and tocopherol (abstract, Example 4 and col. 14, lines 42-63).

It would have been obvious to one of ordinary skill in the art to prepare unilamellar liposomes of claimed sizes encapsulating the salicylic acid acetate with a reasonable expectation of success based on the teachings of Tremblay or Kelemen. It is unclear from these references whether salts of for ibuprofen, sulindac, piroxicam and

naproxen are also taught. However, from Kelemen's teachings that hydrophilic compounds are encapsulated within the aqueous interior, it would have been obvious to one of ordinary skill in the art to prepare salts of NSAIDs which are hydrophobic, if encapsulation of in the aqueous interior of the liposomes is desired. One of ordinary skill in the art would be motivated further to encapsulate salts within the aqueous interior especially in view of Sheffield who teaches the encapsulation of sodium salt of ibuprofen using an aqueous solution (phosphate buffered saline) and hydrating distearoyl phosphatidylcholine (Example 13). Transporting the NSAID across the skin would have been obvious to one of ordinary skill in the art since Tremblay teaches the topical mode of application. The addition of antioxidants and stabilizers in the compositions would have been obvious to one of ordinary skill in the art since such an addition would prevent oxidation of lipids and degradation by bacteria respectively as taught by Mezei. Kelemen, Tremblay and Sheffield also lack the teaching of the application of the claimed amount of the liposomes on the skin surface. However, since the amount applied depends upon the condition to be treated and the severity of the condition, it is deemed obvious to one of ordinary skill in the art to manipulate this parameter to obtain the best possible results.

4. Claims 106, 112-115, 118 and 120-121, 123-124, 129-136 and 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelemen (5,716,526), Tremblay (5,783,210) individually or in combination, optionally in further with Sheffield (4,937,254), in further combination with Mezei (4,897,269) as set forth above, further in view of Weiner (5,049,392).

The teachings of Kelemen, Tremblay, Sheffield and Mezei have been discussed above. As pointed out above, it is unclear from the references of Kelemen and Tremblay whether salts of for ibuprofen, sulindac, piroxicam and naproxen are also taught.

Weiner while disclosing liposomal formulations containing indomethacin, salicylic acid acetate, ibuprofen, sulindac, piroxicam and naproxen teaches that it is desirable to convert lipophilic agents to soluble forms such as soluble salts (col. 7, line 58 through col. 8, line 5).

It would have been obvious to one of ordinary skill in the art to convert the hydrophobic NSAIDs to soluble salts since Weiner is suggestive of such a conversion in liposomes.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK